Published in final edited form as:
Am J Med Genet A. 2008 October 1; 146A(19): 2501–2511. doi:10.1002/ajmg.a.32476.

Agenesis and Dysgenesis of the Corpus Callosum: Clinical, Genetic and Neuroimaging Findings in a Series of 41 Patients

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Abstract

Agenesis of the corpus callosum (ACC) is among the most frequent human brain malformations with an incidence of 0.5–70 in 10,000. It is a heterogeneous condition, for which several different genetic causes are known, for example, ACC as part of monogenic syndromes or complex chromosomal rearrangements. We systematically evaluated the data of 172 patients with documented corpus callosum abnormalities in the records, and 23 patients with chromosomal rearrangements known to be associated with corpus callosum changes. All available neuroimaging data, including CT and MRI, were re-evaluated following a standardized protocol. Whenever feasible chromosome and subtelomere analyses as well as molecular genetic testing were performed in patients with disorders of the corpus callosum in order to identify a genetic diagnosis. Our results showed that 41 patients with complete absence (agenesis of the corpus callosum—ACC) or partial absence (dysgenesis of the corpus callosum—DCC) were identified. Out of these 28 had ACC, 13 had DCC. In 11 of the 28 patients with ACC, the following diagnoses could be established: Mowat–Wilson syndrome (n = 2), Walker–Warburg syndrome (n = 1), oro-facial-digital syndrome type 1 (n = 1), and chromosomal rearrangements (n = 7), including a patient with an apparently balanced reciprocal translocation, which led to the disruption and a predicted loss of function in the *FOXG1B* gene. The cause of the ACC in 17 patients remained unclear. In 2 of the 13 patients with DCC, unbalanced chromosomal rearrangements could be detected (n = 2), while the cause of DCC in 11 patients remained unclear. In our series of cases a variety of genetic causes of disorders of the corpus callosum were identified with cytogenetic anomalies representing the most common underlying etiology.

Keywords

agenesis or dysgenesis of the corpus callosum; clinical-genetic study; MR imaging

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INTRODUCTION

The corpus callosum is the major interhemispheric fiber bundle in the brain [Aboitiz and Montiel, 2003], and consists of about 200 million axons in humans, that is, approximately 2–3% of all cortical fibers, thus making it the largest fiber tract within the central nervous system.

Formation of the corpus callosum begins as early as 6 weeks of gestation when axons destined to cross the midline can be seen growing medially within the hemispheres. At 11–12 weeks of gestation, the first fibers cross the midline through the massa commissuralis, which is located between the anterior and hippocampal commissures, to form the corpus callosum. In the developing brain, axon tracts generally form according to a conserved ontogenic sequence as shown in animal models [Hatten, 1999; Mihrshahi, 2006]. Most axon tracts develop along non-neural substrate cells such as glia, which guide the first pioneering axons to their targets [Holley, 1982; Nordlander and Singer, 1982; Norris and Kalil, 1991]. Thus, a number of glial populations have been found to play a role in the development of the corpus callosum. One of these populations, the so-called midline zipper glia, has been shown to guide the process of midline fusion, a necessary event in the run-up of the formation of the corpus callosum [Silver, 1993]. Two other glia populations, a “glial wedge” being formed in the dorsomedial lateral ventricles, and another glial population being formed in the region of the indusium griseum [Shu and Richards, 2001; Lent et al., 2005], have been identified and shown to play important roles in corpus callosum development. Another structure called “midline sling,” mainly consisting of migratory neurons, forms a midline bridge along which callosal axons can grow to reach the contralateral hemisphere. It has been shown that absence of, or damage to, this sling results in agenesis of the corpus callosum [Silver et al., 1982]. By 18–20 weeks of gestation, the corpus callosum has assumed its final shape except that it will continue to thicken and grow caudally.

Agenesis of the corpus callosum (ACC) is one of the most frequent malformations in brain with a reported incidence raging between 0.5 and 70 in 10,000 [Myrianthopolous, 1977; Jeret et al., 1986]. The prevalence in children with developmental problems has been estimated to be as high as 230 in 10,000 [Jeret et al., 1986, 1987]. Two types of ACC can be distinguished morphologically: (1) ACC type 1, in which axons form but are unable to cross the midline; they consecutively form large aberrant fiber bundles known as Probst bundles along the medial hemispheric walls. (2) ACC type 2, in which commissural axons fail to form; therefore, no Probst bundles are found.

Disorders of the corpus callosum can also be observed in association with major malformations of the embryonic forebrain prior to formation of the anlage of the corpus callosum (e.g., holoprosencephaly, HPE).

ACC is a heterogeneous condition, which can be observed either as isolated condition or as one manifestation in the context of a congenital syndrome. Among the most frequent clinical findings in patients with ACC are mental retardation (60%), visual problems (33%), speech delay (29%), seizures (25%), and feeding problems (20%) [Schilmoeller and Schilmoeller, 2000]. Furthermore, even in cases with no developmental delay and normal intelligence mild behavioral or social problems as well as the attention-deficit-hyperactivity disorder (ADHD) have been described [Brown and Paul, 2000; Doherty et al., 2006].

ACC can be caused by exogenous factors, for example, maternal alcohol use during pregnancy [Sowell et al., 2001] or maternal phenylketonuria [Levy et al., 1996] as well as by genetic factors. Several syndromes that include ACC having autosomal-dominant, autosomal-recessive and X-linked inheritance have been recognized [Dobyns, 1996; Online Mendelian Inheritance in Man (OMIM), 2008], and several causative gene mutations have been identified so far (Table I). In addition, ACC has been observed in constitutional trisomies as well as in

some chromosomal rearrangements like del(4)(p16), del(6)(q23), dup(8)(p21p23), dup(11)(q23qter), suggesting that causative genes may be located in these chromosomal regions (Table II).

On the other hand, cases with isolated ACC and developmental delay without detectable chromosomal changes have also been published with apparent autosomal dominant, autosomal recessive or X-linked modes of inheritance. To our knowledge, causative genes have not been found to date [Serur and Jeret, 1988; Dobyns, 1996].

Much is known about ACC being a part of certain conditions (Tables I and II), or in terms of its association with social, behavioral and medical problems [Brown and Paul, 2000;Schilmoeller and Schilmoeller, 2000;Doherty et al., 2006]. In contrast, there is confusion about the terminology concerning partial absence of the corpus callosum (DCC), where various desgnations are used including hypogenesis, hypoplasia or partial agenesis. In fact, radiological terminology to describe corpus callosum abnormalities used in literature is rather confusing and heterogeneous. For the purpose of this study, only complete absence of the corpus callosum was addressed as agenesis (ACC), and partial absence of the corpus callosum as dysgenesis (DCC). This reflects on the findings by Rubinstein et al. [1994] that the partial appearance of the corpus callosum may be due to a process to overcome initial abnormalities of midline structures resulting in a variety of shape, size and location of an observed callosal structure not necessarily corresponding to a “normal” corpus callosum.

We were interested in finding out, whether we could relate the ACC and DCC seen in patient series classified using a standardized protocol for describing the available neuroimaging to certain underlying genetic causes. Our purpose was to uncover unknown chromosomal regions associated with, or other changes contributing to ACC and DCC.

METHODS

In this retrospective study, data of children seen in our institution for suspected disorders of the corpus callosum between 1984 and 2006 were reviewed. A total of 172 patients were identified in whom corpus callosum abnormalities were documented in the files (group 1). According to our records, the corpus callosum was completely absent in 63 patients and partially absent in 28 patients. In another eight patients the corpus callosun was missing due to holoprosencephaly (HPE), and 73 patients had a corpus callosal hypoplasia (CH).

Another 23 patients (group 2) were added to the study, when seen in our institution, with chromosomal rearrangements known to be associated with corpus callosum changes. In total, we identified 195 patients in groups 1 and 2. In a total number of 126 cases, nine computed tomographies (CT) and 117 magnetic resonance images (MRI) of the brain were performed. In 82 cases, in which a corpus callosum abnormality had been described or suspected, either no neuroimaging other than ultrasound had been performed (n = 65) or detailed imaging studies were not available (n = 17).

In all 126 cases with available neuroimaging, the images were re-evaluated using a standardized protocol focusing on midline and cortical defects by a neuroradiologist specialized in pediatric neuroradiology. In this structured evaluation only complete absence of the corpus callosum was addressed as agenesis (ACC), and partial absence of the corpus callosum as dysgenesis (DCC) [Rubinstein et al., 1994].

In 43 cases, the previous corpus callosum findings were revised: Three times from ACC to DCC, five times from ACC to corpus callosum hypoplasia (CH), four times from DCC to CH, four times from DCC to ACC, once from CH to ACC, five times from CH to DCC, once from CH to HPE, and once from HPE to DCC. Nineteen patients, who had previously been described

to have ACC (n = 2), DCC (n = 3), HPE (n = 1), or CH (n = 13) had no corpus callosum abnormalities at all.

Of the 35 patients with ACC, 28 were seen by a clinical geneticist. In the seven remaining cases, an appointment was offered, but the parents declined. Of the 18 patients with DCC, 13 were seen by a clinical geneticist. In the five remaining cases an appointment was offered, but the parents either declined (n = 4) or were lost to follow-up.

Clinical genetic investigation of a patient included a thorough phenotype assessment including minor anomalies of head, neck, skin, and extremities. Genetic laboratory investigation included chromosome and subtelomeric analyses. For the purpose of this study, a diagnosis was considered chromosomal only, if an unbalanced karyotype was either in conventional, subtelomeric or array-CGH analysis. According to the obtained genetic data and/or a clinically suspected diagnosis, further investigation (e.g., particular gene analysis, microarray-based comparative genomic hybridization in case of severe mental retardation and/or dysmorphic phenotype) was considered and offered.

Array-CGH analysis using a whole genome tiling path BAC array was performed as described previously [Klopocki et al., 2006]. In brief, patient and reference DNA were labeled using a Bioprime CGH labeling kit (Invitrogen, Karlsruhe, Germany) and hybridized on the array (SlideBooster, Implen, Munich, Germany). Analysis and visualization were performed with CGHPRO software. Copy number changes were determined by a conservative $\log_2$ ratio threshold (gain ≥ 0.3; loss ≤ -0.3). Profile deviations consisting of three or more neighboring BACs are considered as genomic aberrations.

RESULTS

After the neuroradiological re-assessment, 110 patients were identified with distinctive features of the corpus callosum:

Thirty-five patients with ACC (34 from group 1 and one from group 2).

Eighteen patients with DCC (all from group 1).

Fifty patients with CH (47 from group 1 and 3 from group 2).

Seven patients with HPE (all from group 1).

Of the 35 patients with ACC, 28 were seen by a clinical geneticist, two of them being brother (A-13) and sister (A-11), and the following diagnoses were established:

Mowat–Wilson syndrome (n = 2; OMIM #235730).

Walker–Warburg syndrome (n = 1; OMIM #236670).

Oro-facial-digital syndrome type 1(n = 1; OMIM #311200).

Six chromosomal changes (only one of them (A-14) being from group 2).

An additional patient had an apparently balanced reciprocal translocation, which led to the disruption and a predicted loss of function of a gene (*FOXG1B* gene), which had not been described previously [Shoichet et al., 2005]. In a total of 19 patients subtelomeric chromosome analyses were performed with normal results.

Of the 18 patients with DCC, 13 were seen by a clinical geneticist, and two chromosomal rearrangements were found (none of the patients were from group 2). In 12 cases subtelomeric analyses were performed, which revealed an unbalanced karyotype in one case. Beside the two siblings (A-13, A-11) with ACC, no other patients were related.

Seventeen patients with ACC and two patients with DCC showed Probst bundles, while in nine patients with ACC and nine patients with DCC Probst bundles were absent. In two cases with ACC and two cases with DCC it remained unclear due to insufficient image quality whether Probst bundles are present or not. A repeat MRI was declined by the parents.

Associated cortical malformations were frequent in our study population:

- polymicrogyria was noted in eight patients with ACC (29%) and in one patient with DCC,
- pachygyria/incomplete lissencephaly was seen in nine patients with ACC (25%) and in one patient with DCC, and
- heterotopia was noted in four patients with ACC (14%) and in one patient with DCC.

Dandy–Walker malformation, Chiari malformation or delayed myelination constituted less frequent findings (Table III).

In 11 of 28 patients with ACC seen by a geneticist, a genetic diagnosis could be established—in the remaining 18 cases the genetic basis of the ACC remained unknown (Table IV). Five cases had non-chromosomal diagnoses:

- Two boys (A-12, A-26) had Mowat–Wilson syndrome (OMIM #235730): One of them (A-12), who was $1\frac{3}{12}$ years old at the time of investigation, had a *de novo* deletion of two base pairs in exon 5 (nt553-554) of the *ZFHX1B* gene. The other one (A-26), who was $1\frac{7}{12}$ years old at the time of investigation, had a de novo deletion of a single nucleotide (nt2176) of the same gene leading to a truncated polypeptide.
- One girl (A-28), who was $8\frac{3}{12}$ years old at the time of investigation, clinically had an oro-facial digital syndrome type 1 (OMIM #311200), which was confirmed by molecular genetic analysis of the *CXORF5* gene revealing a frameshift mutation in exon 5 of the gene not found in the girl's mother.
- Another female patient (A-23) first seen at the age of 14 months by a clinical geneticist, had an apparently balanced translocation t(2;14)(p22;q13) leading to a disruption of the *FOXG1B* gene at the breakpoint of chromosome 14 published by Shoichet et al. [2005].
- A male patient (A-19) with Walker–Warburg syndrome (OMIM #236670), who had a congenital hydrocephalus, dysplastic cortex with agyria, optical atrophy, retinal hemorrhage, and congenital muscular dystrophy, passed away at the age of 9 months. Unfortunately, no samples were available to perform further genetic testing besides chromosome analysis which was normal.

Six cases with ACC, mental retardation, and dysmorphic features had various chromosomal changes:

- A $10\frac{7}{12}$-year-old boy (A-07) had a mosaicism in fibroblast culture with a karyotype of 46,XY[19]/46,XY,del(18)(pter → q21:)[31], but a normal karyotype of 46,XY in lymphocytes.
- A $1\frac{8}{12}$-year-old boy (A-15) had partial monosomy 3p with karyotype 46,XY,del(3)(pter→ p25).
- A $6\frac{3}{12}$-year-old boy (A-24) had trisomy 8 mosaic, karyotype 46,XY[7]/47,XY, +8[93].
- A 13-month-old boy (A-20) with severe mental retardation, macrocephaly, hearing impairment and dysmorphic appearance had trisomy 8pter → 8q11.1 and trisomy 12q11.1 → 12pter mosaic due to a de novo translocation 8p;12p resulting in a dicentric marker chromosome, karyotype 47,XY, +dic(8;12)(8pter → 8q11.1::12q11.1 → 12pter)[28]/ 46,XY[72].

A 9-year-old female patient (A-14) had a partial trisomy 8p in combination with a partial monosomy of the very distal region of 8p due to an inverted duplication 8p23.1 → p11.2 with a deletion of 8p23.1 → pter.

In a $3\frac{5}{12}$-year-old male patient (A-16) with ACC, severe mental retardation, seizures, and dysmorphic features, who had delayed myelination as well as a complex malformation of cortical development with pachygyria and polymicrogyria, chromosome and subtelomeric analyses were performed with normal results. In this case, we additionally applied a whole genome tiling path BAC array in order to investigate the genomic DNA for submicroscopic aberrations. We detected two genomic aberrations: a duplication of 6q25.3-q26 as well as a duplication of 11q25. While the duplication 6q has been classified as a genomic variant (database of genomic variants, version December 13, 2005; http://projects.tcag.ca/variation/), the 230 kb duplication of 11q has not been described as genomic variant yet (Fig. 1). The parents of the patient were investigated as well, both showing no duplication of 11q25.

In 2 of 13 patients with DCC a chromosomal diagnosis could be established (Table IV):

A $2\frac{9}{12}$-year-old girl (D-01) had a partial trisomy 11q and a partial monosomy 6q due a translocation (6;11) revealed by subtelomeric analysis, karyotype: 46,XX,ish der(6)t(6;11)(6qtel-,11qtel+). Analyses of the parents revealed that the child's mother carried a balanced translocation involving chromosomes 6, 11 and 14. Breakpoints were refined by chromosome microdissection showing karyotype: 46,XX,rev ish t(6;11;14) (6pter → q26::11q23.3 → qter; 11pter → q23.3::14q22 → qter; 14pter → q22::6q26→qter).

Another 12-month-old female patient (D-11) had a partial monosomy 7q, karyotype 46,XX,del (7q32 → qter). Remarkably, *Sonic Hedgehog*, one of the major genes accounting for HPE and midline defects in brain, is located in region 7q36.

The major clinical findings of all the patients with ACC and DCC are summarized in Tables V and VI. Findings present in a patient were marked with "+," traits absent with "−" If information concerning a particular trait was not informative, a question mark (?) was used.

The two siblings A-13 and A-11 with ACC, were listed and counted individually because they were discordant for major clinical findings, though they are likely to have a common genetic etiology for the corpus callosum abnormality. The female patient A-11 had a developmental delay and muscular hypotonia. Her brother A-13 developed normally and was healthy. The ACC in his case was revealed by chance due to a postnatal ultrasound. The differences between these siblings may be due to a different genetic background modifying a common genetic cause for ACC, which could be also gender specific, or the corpus callosum changes and the associated clinical findings have in fact different genetic or even non genetic causes in both of these two children.

Concerning the patients with ACC, 25 out of 28 (89%) had a developmental delay. Twenty-one of 24 patients (88%) had a delay in speech development and 21 of 25 patients (84%) had feeding problems. Fifteen of 25 patients (60%) had visual problems, and three of 17 (18%) were hearing impaired. Thirteen of 21 patients (62%) developed seizures, 21 out of 23 (91%) had abnormal muscular tone.

Concerning the patients with DCC, all had developmental delay, and a delay in speech development and eight out of 13 patients (62%) had feeding problems. Eight of 12 patients (67%) had visual problems, and one of 11 (10%) were hearing impaired. Eight of nine patients (89%) developed seizures, 10 out of 12 (83%) had abnormal muscular tone.

Only slightly different frequencies of the major clinical findings were found, when patients without specific diagnosis are taken separately. These findings including the frequencies are

given in Tables VII and VIII. Concerning the patients with ACC without a diagnosis, 14 out of 17 (82%) had a developmental delay. Twelve of 15 patients (80%) had a delay in speech development and 11 of 15 patients (73%) had feeding problems. Eight of 15 patients (57%) had visual problems, nine of 13 patients (69%) developed seizures, and 11 out of 13 (85%) had abnormal muscular tone.

Concerning the patients with DCC, 6 out of 10 patients (60%) had feeding and/or visual problems, 7 of 8 patients (89%) developed seizures, and 8 out of 10 (88%) had abnormal muscular tone.

Interestingly none of these patients with ACC, and only one out of 10 patients with DCC (10%) was hearing impaired, suggesting that hearing problems were part of the specific diagnoses in the other patients.

DISCUSSION

Since ACC is one of the most frequent brain malformations in children with developmental delay it is crucial to establish consistent criteria in the radiological assessment of the corpus callosum description in order to achieve reproducible and comparable results. In this study, we decided to include only patients with complete absence of the corpus callosum (ACC), or partial absence (dysgenesis) of the corpus callosum (DCC), based on the terminology that has been introduced by Rubinstein et al. [1994]. Known genetic causes for the absence of the corpus callosum are chromosomal rearrangements and several genetic disorders with autosomal dominant, autosomal recessive and X-linked mode of inheritance (see also Tables I and II).

The results of our study confirmed data known from the literature, and moreover added to the current knowledge (Table IX). In the case of patient A-16, where array-CGH analysis revealed a 230 kb spanning de novo microduplication in 11q25. This has not been described as genomic variant before (see also Fig. 1) and was not present in the patient's parents. In the light of partial trisomy of the region 11q23 → qter is known to be involved in ACC [Rott et al., 1972] this finding is suggestive that the region in this patient is the smallest region of overlap described so far involved in corpus callosum formation (see also Fig. 1). In the case of A-23, who had a cytogenetically balanced translocation t(2;14)(p22;q13), we were able to show that this rearrangement led to a disruption of the *FOXG1B* gene at the breakpoint of chromosome 14 [Shoichet et al., 2005]. As the chromosomal region 14q13 is known to be involved in HPE formation [Kamnasaran et al., 2005], the *FOXG1B* gene could be a good candidate not only for ACC but for HPE as well.

Interestingly, in none of the patients with DCC a non-chromosomal diagnosis could be established. In six out of 28 patient with ACC a chromosomal change was found, but only in two out of 13 patients with DCC, one of these identified with subtelomeric analysis, suggesting that DCC is not seen in complex chromosomal and non-chromosomal disorders.

As mentioned before, the most common clinical findings in patients with ACC are described in the literature to be mental retardation (60%), visual problems (33%), speech delay (29%), seizures (25%), abnormal muscular tone (25%), and feeding problems [Schilmoeller and Schilmoeller, 2000]. Though the study of Schilmoeller and Schilmoeller [2000] involved more patients than in the present study (596 families from the US and 12 other countries provided dermographic information, and a profile of their child by completing a questionnaire), the approach was completely different from our study, and, therefore, comparing results and frequencies is difficult: In the study reported by Schilmoeller and Schilmoeller [2000] all information on patients were collected merely on the basis of a questionnaire completed by the families themselves and not by professionals. Consistent clinical investigation was not offered and performed in the patients and Magnetic Resonance Imaging was not performed in all of

them (only in 33.3%); neuroimaging was not evaluated according to standardized criteria. Therefore, the higher frequencies for these features found in the present study may be due to different usage both of the radiological terminology, and of the diagnostic criteria underlying the assessment and evaluation of the particular clinical features. Unfortunately, Schilmoeller and Schilmoeller [2000] did not report on genetic or biological causes of the patients as well.

There are several limitations in our study that need to be taken into account when interpreting the data. Recent neuroimaging data were not available in all patients. As our study included exclusively patients, in whom corpus callosum abnormalities had previously been reported in the files, it remains unknown how many patients seen in our institution actually had a pathology of the corpus callosum. It is known that even patients with normal intelligence, mild behavioral or social problems as well as the attention-deficit-hyperactivity disorder (ADHD) may have ACC [Brown and Paul, 2000; Doherty et al., 2006].

Though the genetic basis of the complete and partial absence of the corpus callosum was identified in 13 of 41 patients (32%), the cause remained unknown in 68%. Further studies need to be performed to elucidate the genetic and biological bases of corpus callosum formation, and its complete or partial absence as well as associated brain malformation, and clinical findings.

Acknowledgments

We sincerely thank the patients and their families for participation in this study, M. Wettwer for performing the chromosome and subtelomere analyses, R. Ullmann and the Max-Planck-Institute of Molecular Genetics, Berlin, for providing the BAC array for array-CGH analysis as well as F. Trotier for her technical assistance. This work was supported by the Else Kroener-Fresenius Foundation.

Grant sponsor: Else Kroener-Fresenius Foundation.

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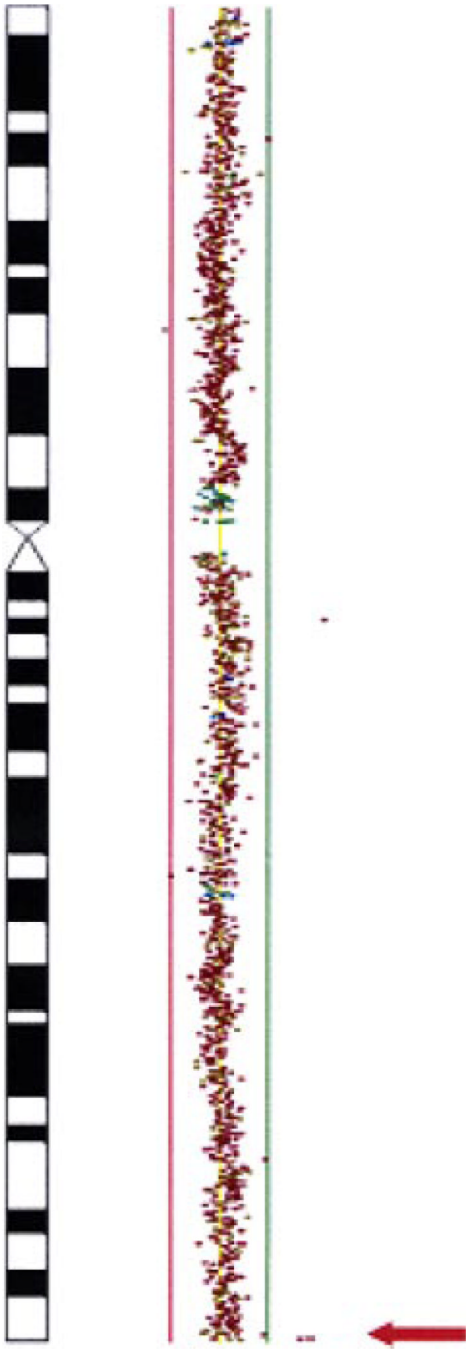

Fig. 1.

Array CGH profile of chromosome 11 of patient A-16 showing a de novo microduplication 11q25 not described as a genomic variant yet. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

TABLE I

Complex Genetic Syndromes With Agenesis of the Corpus Callosum (ACC) as a Possible Feature

Syndrome	Chromosomale region	Gen	OMIM#
Autosomal-dominant			
Apert syndrome	10q26	FGFR2	#101200
Basal cell nevus syndrome	9q22.3	PTCH	#109400
Greig cephalopolysyndaktyly syndrome	7p13	GLI3	#175700
Miller–Dieker syndrome	17p13.3	LIS1	#247200
Mowat–Wilson syndrome	2q22	ZFHX1B	#235730
Opitz GBBB syndrome	22q11.2		%145410
Rubinstein–Taybi syndrome	16p13.3	CREBBP	
	22q13	EP300	#180849
Autosomal-recessive			
Acrocallosal syndrome	7p13	GLI3	#200990
Andermann syndrome	15q13-q14	SLC12A6	#218000
Coffin–Siris syndrome			135900
Dincsoy syndrome			601016
Fryns syndrome			%229850
Fukuyama congenital muscular dystrophy	9q31	FCMD	#253800
Hydrolethalus syndrome	11q23-q25		%236680
	9q34.3		%213300
Joubert syndrome	6q23.2-q23.3	AHI1	#608629
Lowry–Wood syndrome			%226960
Lyon syndrome			225740
Marden–Walker syndrome			%248700
Meckel–Gruber syndrome	17q22-q23		%249000
Microcephalic osteodysplastic primordial dwarfism, type 1			%210710
Microcephalic osteodysplastic primordial dwarfism, type 3			%210730
Muscle-eye-brain disease	1p34-p33	POMGNT1	#253280
Neu–Laxova syndrome			%256520
Ocular motor apraxia (Cogan-syndrome)	2q13		%257550
Peters-Plus syndrome			%261540
Septooptic dysplasia	3p21.2-p21.1	HESX1	#182230
Toriello–Carey syndrome			%217980
Vici syndrome			%242840
	9q34.1	POMT1	
	14q24.3	POMT2	
Walker–Warburg syndrome	9q31	FCMD	#236670
Warburg–Mikro syndrome	2q21.3	RAB3GAP	#600118
X-linked			
ACC in combination with ectodermal dysplasia (hypohidrotic)			225040
Aicardi syndrome	Xp22		%304050
ATR-X syndrome	Xq13	ATRX	#301040
FG syndrome	Xq12-q21.31		%305450
X-linked aqueductal stenosis or hydrocephalus/MASA syndrome	Xq28	L1CAM	#307000
Craniofrontonasal syndrome	Xq12	EFNB1	#304110
Lujan–Fryns syndrome			%309520
MLS syndrome	Xp22.31		%309801
Opitz GBBB syndrome	Xp22	MID1	#300000
Oro-facial digital syndrome type 1	Xp22.3-p22.2	CXORF5	#311200
Proud syndrome	Xp22.13	ARX	#300004
X-linked lissencephaly	Xq22.3-q23	DCX	#300067

TABLE II

Chromosomal Rearrangements With Agenesis of the Corpus Callosum as a Possible Feature

Region	Karyotype, SRO = smallest region of overlap
Deletions and translocations	
1q44qter	SRO
1q43	del(1)(q43)
1q43qter	del(1)(q43)^{n}
1q44qter	–21,der(1),t(1;21)(q44;q22.11)
2q14	SRO
2q12q14	del(2)(q12q14)
2q14q21	del(2)(q14q21)
2q31	SRO
2q22q31	del(2)(q22q31)
2q31q33	del(2)(q31q33)
3p25pter	del(3)(p25pter)
4p16	SRO
4p16	del(4)(pterp16.1)
6q23qter	SRO
6q23qter	del(6)(q23)
6p2/q2	r(6)/(p2?q2?)
7q32qter	del(7)(q32qter)
15q13	SRO
15q13	t(2;15)(p21;q13)
15q13q15	del(15)(q13q15)
16q22qter	rec(16),dup p, inv(16)(p12.1q22)
18q21qter	del(18)(q21qter)
21q11q21	SRO
21	Monosomie 21 Mosaik
21pterq22.1	–21,der(1),t(1;21)(q44;q22.11)
21pterq21	–21,der(20),t(20;21)(q13;q21)
Xp22.3	SRO
Xp22.3	del(X)(p22.3)
Xq13q21	del(X)(q13q21.3)
Duplication	
Triploidy	Triploidy (mosaicism)
5p13.1p15.3	SRO
5p11pter	der(15),t(5;15)(p11;p12)
5p13.1p15.3	inv dup(5)(p13.1p15.3)
6p25pter	SRO
6p25pter	der(3),t(3;6)(q29;p21.1)mar
6p25pter	dup(6)(p25)
6q25qter	dup(6)(q25qter)
8p21p23	SRO
8	Trisomy 8 mosaicism
8p11pter	i(8p)mos
8p11pter	der(15),t(8;15)(p11;p15)pat
8p21pter	dup(8)(p21pter)
8p21pter	der(10),t(8;10)(p21;p15)
8p21pter	dup(8)(p21)/del(8)(p21)
8p11p23.1	dup(8)(p11p23.1)
8p11.2p23.1	dup(8)(p11.2p23.1)(?)
8p23qter	–8,+idic(8)(p23)
8p11p22	dup(8)(p11p22)
11q23qter	SRO
11q14.2qter	der(18),t(11;18)(q14.2;p11.31)
11q21.1qter	der(4),t(4;11)(q35;q21.1)
11q23qter	der(13),t(11;13)(q13;q32-34)
11q23.1qter	der(4),t(4;11)(q35;q32.1)mat
14q23q24	SRO
14pterq24	+der(14),t(3;14)(p26;q24)
14q23q32	–5,+der(5),ins(5;14)(q13;q23q32)
19q13.2qter	der(13),t(13;19)(p13;q13.2)

TABLE III

Summary of MRI Results of 28 Patients With Agenesis of the Corpus Callosum (ACC) and 13 Patients With Dysgenesis of the Corpus Callosum (DCC)

	ACC (N = 28)	DCC (N = 13)
Probst bundles present	17	2
Probst bundles absent	9	9
Probst bundles indeterminate	2	2
Polymicrogyria	8/28	1/13
Pachygyria/lissencephaly	9/28	1/13
Heterotopia	4/28	1/13
Dandy–Walker malformation	0/28	2/13
Chiari malformation	1/28	0/13
Delayed myelination	3/28	2/13

TABLE IV

Outcome of Elaborated Genetic Diagnoses in 41 Patients With Agenesis (ACC) or Dysgenesis (DCC) of the Corpus Callosum

Patients with ACC	Patients with DCC	
Non-chromosomal diagnosis		
A-12 (Mowat–Wilson syndrome)		13/41 = 32%
A-19 (Walker–Warburg syndrome)		
A-23 (FOXG1B-gene mutation)		
A-26 (Mowat–Wilson syndrome)		
A-28 (Oro-facial-digital synd. type 1)		
Chromosomal changes		
A-07 (part. monosomy 18q-mosaic)	D-01 (part. Mon. 6q + part. Tris. 11q)	
A-14 (inv dup(8p)	D-11 (part. Monosomie 7q)	
A-15 (part.monosomy 3p)		
A-16 (microduplication 11q25, polymorphism ?)		
A-20 (trisomy 8p + 12p-mosaic)		
A-24 (trisomy 8 mosaic)		
Cause yet unkown		
A-01	D-02	28/41 = 68%
A-02	D-03	
A-03	D-04	
A-04	D-05	
A-05	D-06	
A-06	D07	
A-08	D-08	
A-09	D-09	
A-10	D-10	
A-11	D-12	
A-13	D-13	
A-17		
A-18		
A-21		
A-22		
A-25		
A-27		

TABLE V

Summary of the Major Clinical Findings of All the Patients With Agenesis of the Corpus Callosum (ACC)

Patient	M/F	Age at last exam	Developmental delay	Speech delay	Feeding problems	Visual problems	Hearing impairment	Seizures	Abnormal muscular tone
A-01	M	$5\frac{9}{12}$ years	+	?	+	?	?	+	+
A-02	M	$2\frac{9}{12}$ years	+	+	+	–	?	?	+
A-03	F	$4\frac{1}{12}$ years	+	+	?	+	–	+	+
A-04	F	$9\frac{9}{12}$ years	+	+	+	–	?	?	+
A-05	M	$6\frac{2}{12}$ years	+	+	?	+	–	–	?
A-06	M	5 years	+	+	+	+	–	+	+
A-07	M	$10\frac{7}{12}$ years	+	+	+	+	?	+	+
A-08	F	$22\frac{7}{12}$ years	–	–	+	+	–	+	?
A-09	F	$8\frac{4}{12}$ years	+	+	+	+	–	+	+
A-10	F	$2\frac{4}{12}$ years	+	+	+	–	?	–	+
A-11	F	12 months	+	?	+	–	?	–	+
A-12	M	15 months	+	+	+	+	?	–	+
A-13	M	3 years	–	–	+	–	–	?	?
A-14	F	9 years	+	+	+	–	?	–	+
A-15	M	20 months	+	+	+	+	+	–	+
A-16	M	$3\frac{5}{12}$ years	+	+	+	+	–	–	+
A-17	M	$8\frac{8}{12}$ years	–	–	–	–	–	+	–
A-18	F	$10\frac{8}{12}$ years	+	+	–	?	–	–	+
A-19	M	$7\frac{1}{12}$ years	+	?	+	+	?	+	+
A-20	M	13 months	+	?	+	+	+	?	+
A-21	M	$8\frac{8}{12}$ years	+	+	–	+	–	+	+
A-22	M	16 months	+	+	+	+	?	+	+
A-23	F	14 months	+	+	+	–	–	+	+
A-24	M	$6\frac{3}{12}$ years	+	+	?	–	–	?	–
A-25	F	$16\frac{6}{12}$ years	+	+	+	?	?	+	?
A-26	M	19 months	+	+	+	+	–	?	+
A-27	M	18 months	+	+	–	+	–	?	?
A-28	F	$8\frac{3}{12}$ years	+	+	+	–	+	+	+
			25/28 89%	21/24 88%	21/25 84%	15/25 60%	3/17 18%	13/21 62%	21/23 91%

M: male; F: female; +: trait present; –: trait not present; ?: information not informative concerning this trait.

TABLE VI

Summary of the Major Clinical Findings of All the Patients With Dysgenesis of the Corpus Callosum (DCC)

Patient	M/F	Age at last exam	Developmental delay	Speech delay	Feeding problems	Visual problems	Hearing impairment	Seizures	Abnormal muscular tonus
D-01	F	$2\frac{9}{12}$ years	+	+	+	+	–	+	+
D-02	F	$4\frac{10}{12}$ years	+	+	–	+	–	?	+
D-03	F	$8\frac{1}{12}$ years	+	+	+	–	–	+	+
D-04	F	$7\frac{11}{12}$ years	+	+	?	–	+	?	–
D-05	F	$9\frac{11}{12}$ years	+	+	–	+	–	?	+
D-06	M	4 years	+	+	+	+	–	+	+
D-07	M	$11\frac{1}{12}$ years	+	+	–	+	–	+	?
D-08	M	$7\frac{11}{12}$ years	+	+	+	+	–	+	–
D-09	M	$11\frac{4}{12}$ years	+	+	+	+	–	+	+
D-10	F	$8\frac{6}{12}$ years	+	+	+	?	?	+	+
D-11	F	12 months	+	+	+	+	?	?	+
D-12	F	$5\frac{6}{12}$ years	+	+	+	–	–	+	+
D-13	F	$9\frac{10}{12}$ years	+	+	–	–	–	–	+
			13/13 100%	13/13 100%	8/13 62%	8/12 67%	1/11 10%	8/9 89%	10/12 83%

M: male; F: female; +: trait present; –: trait not present; ?: information not informative concerning this trait.

TABLE VII

Summary of the Major Clinical Findings of the Patients With Agenesis of the Corpus Callosum (ACC) without Specific Diagnosis

Patient	M/F	Age at last exam	Developmental delay	Speech delay	Feeding problems	Visual problems	Hearing impairment	Seizures	Abnormal muscular tone
A-01	M	$5\frac{9}{12}$ years	+	?	+	?	?	+	+
A-02	M	$2\frac{9}{12}$ years	+	+	+	–	?	?	+
A-03	F	$4\frac{1}{12}$ years	+	+	?	+	–	+	+
A-04	F	$9\frac{9}{12}$ years	+	+	+	–	?	?	+
A-05	M	$6\frac{2}{12}$ years	+	+	?	+	–	–	?
A-06	M	5 years	+	+	+	+	–	+	+
A-08	F	$22\frac{7}{12}$ years	–	–	+	+	–	+	?
A-09	F	$8\frac{4}{12}$ years	+	+	+	+	–	+	+
A-10	F	$2\frac{4}{12}$ years	+	+	+	–	?	–	+
A-11	F	12 months	+	?	+	–	?	–	+
A-13	M	3 years	–	–	+	–	–	?	–
A-17	M	$8\frac{8}{12}$ years	–	–	–	–	–	+	–
A-18	F	$10\frac{8}{12}$ years	+	+	–	?	–	–	+
A-21	M	$8\frac{8}{12}$ years	+	+	–	+	–	+	+
A-22	M	16 months	+	+	+	+	?	+	+
A-25	F	$16\frac{6}{12}$ years	+	+	+	?	?	+	?
A-27	M	18 months	+	+	–	+	–	?	?
			14/17 82%	12/15 80%	11/15 73%	8/14 57%	0/10 0%	9/13 69%	11/13 85%

M: male; F: female; +: trait present; –: trait not present; ?: information not informative concerning this trait.

TABLE VIII

Summary of the Major Clinical Findings of the Patients With Dysgenesis of the Corpus Callosum (DCC) without Specific Diagnosis

Patient	M/F	Age at last exam	Developmental delay	Speech delay	Feeding problems	Visual problems	Hearing impairment	Seizures	Abnormal muscular tonus
D-02	F	$4\frac{10}{12}$ years	+	+	–	+	–	?	+
D-03	F	$8\frac{1}{12}$ years	+	+	+	–	–	+	+
D-04	F	$7\frac{11}{12}$ years	+	+	?	–	+	?	–
D-05	F	$9\frac{11}{12}$ years	+	+	–	+	–	?	+
D-06	M	4 years	+	+	+	+	–	+	+
D-07	M	$11\frac{1}{12}$ years	+	+	–	+	–	+	?
D-08	M	$7\frac{11}{12}$ years	+	+	+	+	–	+	–
D-09	M	$11\frac{4}{12}$ years	+	+	+	+	–	+	+
D-10	F	$8\frac{6}{12}$ years	+	+	+	?	?	+	+
D-12	F	$5\frac{6}{12}$ years	+	+	+	–	–	+	+
D-13	F	$9\frac{10}{12}$ years	+	+	–	–	–	–	+
			11/11 100%	11/11 100%	6/10 60%	6/10 60%	1/10 10%	7/8 89%	8/10 88%

M: male; F: female; +: trait present; –: trait not present; ?: information not informative concerning this trait.

TABLE IX

Established Non-Chromosomal (a) and Chromosomal Diagnoses (b) in 12 Patients With Underlying Cause

Established non-chromosomal diagnoses in this study	Patient	Result of the genetic test
(a)		
Mowat–Wilson syndrome [Zweier et al., 2002]	A-12	Frameshift mutation in the ZFHX1B gene
	A-26	Frameshift mutation in the ZFHX1B gene
Walker–Warburg syndrome [Dobyns et al., 1989]	A-19	Unknown, child deceased, no material available
Oro-facial-digital syndrome type 1 [Thauvin-Robinet et al., 2006]	A-28	Frameshift mutation in the CXORF5 gene
FOXG1-B-gene mutation	A-23	Disruption in the gene due to a translocation (2;14)

Established chromosomal diagnoses in this study	Patient	Chromosomal segment known to be involved in ACC formation and reference
(b)		
Partial monosomy 3p25 → pter	A-15	Partial monosomy 3p25 → pter [Mowrey et al., 1993]
Partial monosomy 7q32 → qter	D-11	Partial monosomy 7q32 → qter [Benzacken et al., 1997]
Trisomy 8 mosaicism	A-24	Trisomy 8 mosaicism [Baverel et al., 1985]
Inverted duplication 8p23.1 → p11.2	A-14	Partial trisomy 8p21 → pter [Fineman et al., 1979]
Trisomy 8pter → 8q11.1 + trisomy 12q11.1 → 12pter mosaicism	A-20	Partial trisomy 8p11 → pter [Funderburk et al., 1978]
Partial monosomy 6qter → q26 + partial trisomy 11qter → q23.3	D-01	Partial trisomy 11q23 → qter [Rott et al., 1972]
Microduplication 11q25	A-16	Partial trisomy 11q23 → qter [Rott et al., 1972]
Partial monosomy 18q21 → qter mosaicism	A-07	Partial monosomy 18q21 → qter [Valdamanis et al., 1967]